

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date
28 July 2005 (28.07.2005)

PCT

(10) International Publication Number
WO 2005/068471 A1

(51) International Patent Classification⁷: **C07D 495/04 //**
(C07D 495/04, 333:00, 221:00)

PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(21) International Application Number:

PCT/CZ2004/000089

(22) International Filing Date:

21 December 2004 (21.12.2004)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

PV 2004-61 13 January 2004 (13.01.2004) CZ
PV 2004-1192 7 December 2004 (07.12.2004) CZ

(71) Applicant (for all designated States except US): ZENTIVA, A.S. [CZ/CZ]; U kabelovny 130, Dolini Mocholupy, 102 37 Praha 10 (CZ).

(72) Inventors; and

(75) Inventors/Applicants (for US only): HAJICEK, Josef [CZ/CZ]; Lumirova 2, 120 00 Praha 2 (CZ). PIHERA, Pavel [CZ/CZ]; Limuzská 530/37, 108 00 Praha 10 (CZ). STEPANKOVA, Hana [CZ/CZ]; Na cihelne 1335, 282 01 Cesky Brod (CZ).

(74) Agents: JIROTKOVA, Ivana et al.; Rott, Ruzicka & Guttmann, Patent, Trademark & Law Office, Nad Stolou 12, 170 00 Praha 7 (CZ).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

Declaration under Rule 4.17:

- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

Published:

- with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/068471 A1

(54) Title: NEW CRYSTALLINE FORMS OF CLOPIDOGREL HYDROBROMIDE AND METHODS OF THEIR PREPARATION

(57) Abstract: The invention concerns clopidogrel hydrobromide in the crystalline Form I characterized by an X-ray diffraction pattern with characteristic interplanar distances d of 4.01; 4.39 and 3.17 \AA and which is further characterized by bands in the infrared spectra at 1743; 1421; 1237, 760 and 728 cm^{-1} . Clopidogrel hydrobromide in the crystalline Form II is characterized by an X-ray diffraction pattern with characteristic interplanar distances d of 4.52; 3.83; 3.48 \AA , as well as bands in the infrared spectra at 1754; 1436; 1317 and 1223 cm^{-1} . Crystalline form III is characterized by the following peaks ascertained by X-ray diffraction at 20 positions: 7.796 $^{\circ}$; 15.380 $^{\circ}$; 18.389 $^{\circ}$; 19.369 $^{\circ}$ and 23.895 $^{\circ}$. The method of preparation of clopidogrel hydrobromide in the crystalline Form I consist in precipitating the clopidogrel base dissolved in toluene with a concentrated solution of hydrobromic acid. The method of preparation of clopidogrel hydrobromide in the crystalline Form II consist in dissolving the clopidogrel base in an organic solvent and precipitating it with a solution of hydrobromic acid in toluene or with gaseous hydrogen bromide. Form III can be used for the preparation of pharmaceutically applicable Form II.